BBB Seminar (BMED382)

SCAN ME

Thursday, March 12. 14:30 at the BBB, Auditorium 4

Myelin turnover, maintenance and disease: insight from (volume) electron microscopy

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Investigation of the fine structure of myelin requires the resolution of transmission electron microscopy. With this technique, subtle changes in the characteristics of the myelin sheath in pathological states can be detected. To understand the myelin sheath in its entirety, volume electron microscopy (vEM) is an indispensable tool. By combining conditional knock-out mouse genetics and focused ion beam-scanning electron microscopy (FIB-SEM), fundamental myelin biology can be studied.

To visualize the slow process of myelin turnover at an ultrastructural level, we generated an inducible conditional knock-out of myelin basic protein (MBP). MBP is essential for myelin compaction in the central nervous system (CNS). Depletion of MBP by ablation of the *Mbp* gene after tamoxifen-induced recombination in the adult mouse resulted in a slow demyelination. While compact myelin served as marker for developmentally formed, resident myelin, newly generated myelin membranes remained non-compacted. This structural change revealed that newly formed membranes were added at the inner tongue of the myelin sheath in proximity to the paranode.

Myelinated axons exist in a close metabolic relationship with the myelinating oligodendrocyte. This is highlighted by the impact of genetic defects in oligodendrocytes on neuronal health. Deficiency of the major CNS myelin protein proteolipid protein (PLP) is the cause for spastic paraplegia type 2 (SPG2), an inherited X-linked leukodystrophy. The SPG2 mouse model, the $Plp^{-/Y}$ mouse, displayed disease hallmarks like axonal swellings and progressive length-dependent axonal degeneration. VEM revealed so far undescribed disease-related changes beyond axonal swellings like myelin outfoldings and axonal abnormalities. Deficiency of another protein, myelin-associated glycoprotein (MAG), also induced the formation of similar outfoldings, although these two proteins differ in their structure, function and localization. Such pathological changes in myelinated axons become visible only by vEM techniques.

Chairperson: Petri Kursula, Department of Biomedicine